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Original Article

A comparative analysis of predisposing factors for delirium in hospitalized patients during and after COVID-19 restriction periods

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ABSTRACT

Aims: The COVID-19 pandemic has had a significant impact on hospitalized patients, with delirium emerging as a common and severe complication, especially during periods of strict restrictions. The influence of environmental and psychosocial factors on delirium during different phases of the pandemic remains underexplored. This study aimed to assess the differences in predisposing factors for delirium between the restriction and relaxed periods of the COVID-19 pandemic.

Methods: In this retrospective study, 102 patients diagnosed with delirium between January 2020 and December 2023 were included. Patients were divided into two groups based on their admission periods relative to the COVID-19 pandemic restrictions. Group 1 (n = 64) consisted of patients admitted during the period of strict COVID-19 measures (11 March 2020 – 30 June 2021), while group 2 (n = 38) included those admitted after the restrictions were lifted (1 July 2021 – 30 June 2023). Demographic and clinical data were collected using the hospital's electronic information system and patient files.

Result: The mean age of the patients was 72.4±11.5 years (range: 50 to 92 years), and 51% of them were male. There were no significant differences in the distribution of age, gender, and comorbidities across the two groups. Group 1 had a significantly higher ratio of patients with COVID-19 infection compared to group 2 (60.9% vs. 36.8%, p=0.024). Sleep deprivation was more common in group 1 than in group 2 (87.5% vs. 68.4%, p=0.037). The duration of delirium was significantly longer in group than in group 2 (3 vs. 2 days p=0.045). Patients in group 1 had a significantly longer hospital stay compared to those in group 2 (9 vs. 6 days p<0.001). Although the mortality rate was observed to be higher in group 1 compared to group 2, this difference was not statistically significant (18.8% vs. 10.5%, p=0.400).

Conclusion: During the restriction period of the COVID-19 pandemic, patients with delirium exhibited higher rates of COVID-19 infection, increased sleep deprivation, and longer delirium episodes compared to those during the relaxed period. The prolonged delirium duration and extended hospital stays observed in the restriction period suggest that environmental and psychosocial factors may have contributed to more severe outcomes.

Keywords: COVID-19, delirium, hospitalized patients, infection, pandemic restrictions, predisposing factors, sleep deprivation

INTRODUCTION

The COVID-19 pandemic has had a significant impact on the physical, cognitive, and mental health of individuals, with some experiencing long-term effects even after their initial recovery from the virus. One concerning outcome is the development of delirium, a state of acute confusion and disorientation, which has been observed both during the active phases of COVID-19 infection as well as in the post-recovery period.[1-3]

Delirium is characterized by sudden changes in attention, awareness, and cognitive function, typically caused by an underlying medical condition and not related to any pre-existing neurocognitive disorder.[4] It is frequently observed in elderly hospitalized individuals and ICU patients, with an incidence reported to be between 15% and 50%.[5,6] Several studies have defined risk factors for delirium in COVID-19 patients, including advanced age, male sex, living conditions, prolonged treatment duration, a history of neurodegenerative diseases, and the presence of infections and renal-retention indicators.[7-9] These are often aggravated by pandemic-related stressors, such as social distancing, disrupted routines, and diminished social contact.[10] Furthermore, in COVID-19 survivors, particularly those with severe respiratory failure and prolonged ICU delirium, cognitive impairments, including deficits in memory, attention, and executive function, have been observed.[11]

There have been conflicting reports on the effect of COVID-19 restrictions on delirium. Some studies have indicated that COVID-19 restrictions do not have a significant impact

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on delirium, whereas others have reported an increased risk of delirium due to these restrictions.[12-14] Given these conflicting reports, we hypothesized that predisposing factors contributing to the development of delirium may vary between periods of strict COVID-19 restrictions, characterized by social isolation, reduced social interaction, and limited access to healthcare, and periods when these restrictions were lifted. Therefore, this study aimed to assess the differences in predisposing factors for delirium between the restriction and relaxed periods of the COVID-19 pandemic.

METHODS

Following the principles set forth in the Declaration of Helsinki, this single center retrospective study was conducted at the İstanbul Atlas University Medicine Hospital Neurology Clinical from 1 January 2020 to 1 December 2023. The study received approval from the İstanbul Atlas University Clinical Researches Ethics Committee (Date: 18.12.2023, Decision No: 10/31). The İstanbul Atlas University Ethics Committee waived the requirement of informed consent due to the retrospective nature of the research. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 140 patients diagnosed with delirium were retrospectively examined. The diagnosis of delirium was established based on the DSM-V Delirium Diagnostic Criteria.[15] Eligibility criteria required patients to be over 18 years old, hospitalized for longer than 24 hours, with a Glasgow Coma Scale (GCS) score above 10, non-intubated, and without any neurological or psychiatric diagnoses. Patients suffering from acute ischemic stroke, dementia, epilepsy, undergoing psychiatric treatment, or those admitted to the ICU were excluded. Following the exclusion process, 102 patients were included in the study.

Demographic and clinical data were collected using the hospital's electronic information system and patient files. The first case of COVID-19 in Turkey was identified on March 11, 2020, followed by the implementation of strict measures to combat the pandemic. These measures included mandatory mask-wearing, social isolation, halting of air travel, curfews, shifting to online learning, the temporary closure of cafes and restaurants, and the cancellation of public events. Pandemic measures began to be lifted on June 1, 2021, transitioning the country into a normalcy process after more than a year of restrictions and pandemic management efforts.[16,17] Accordingly, patients were divided into two groups based on their hospital admission dates. Group 1, during the COVID-19 pandemic when strict measures were enforced (11 March 2020–30 June 2021); and group 2, the period after the lifting of COVID-19 pandemic measures (1 July 2021–30 June 2023).

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean ± standard deviation (SD) values while non-normally distributed variables are given as median (25^{th}-75^{th} quartile) values. For comparisons between groups, Student t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULT

The study included 102 patients, comprising 52 females and 50 males, with an age range of 50 to 92 years (mean age: 72.4±11.5 years). Among the patients, 62.7% were hospitalized during the time of strict COVID-19 restrictions (group 1), whereas 37.3% were admitted when the restrictions were relaxed (group 2). In both groups, the leading comorbid conditions were congestive heart failure, hypertension, and diabetes mellitus. There were no significant differences in the distribution of age, gender, and comorbidities across the two groups (Table 1).

Table 1. Demographic characteristics of patients

Variables	COVID-19 pandemic		p
	Restriction period (group 1) n=64	Relaxed period (group 2) n=38	
Age, years	73.3±11.5	70.8±11.4	0.289
Gender, n (%)			
Male	34 (53.1)	18 (47.4)	0.683
Female	30 (46.9)	20 (52.6)	
Marital status, n (%)			
Married	37 (57.8)	28 (73.7)	0.137
Single	27 (42.2)	10 (26.3)	
Comorbidities, n (%)			
Congestive heart failure	43 (67.2)	28 (73.7)	0.515
Hypertension	48 (75.0)	30 (78.9)	0.810
Diabetes mellitus	41 (64.1)	28 (73.7)	0.137
Cognitive disorders	26 (40.6)	17 (44.7)	0.836
Hearing disorders	24 (37.5)	14 (36.8)	0.999
Visual disorders	7 (10.9)	4 (10.5)	0.999
Trauma history, n (%)	9 (14.1)	5 (13.2)	0.999

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%)

Comparison of various clinical and physiological variables between patients hospitalized during the restriction period and those admitted during the relaxed period of the COVID-19 pandemic revealed several notable differences. Group 1 had a significantly higher ratio of patients with COVID-19 infection compared to group 2 (60.9% vs. 36.8%, p=0.024). Sleep deprivation was more common in group 1 than in group 2 (87.5% vs. 68.4%, p=0.037). Although the incidence of hypoxemia was higher in group 2 (71.1%) compared to Group 1 (53.1%), this difference did not reach statistical significance (p=0.096). The duration of delirium was significantly longer in group than in group 2 (3 vs. 2 days p=0.045). Patients in group 1 had a significantly longer hospital stay compared to those in group 2 (9 vs. 6 days p<0.001). Although the mortality rate was observed to be higher in group 1 compared to Group 2, this difference was not statistically significant (18.8% vs. 10.5%, p=0.400). Other variables such as the presence of anemia, hyperglycemia, body temperature abnormalities, renal failure, dehydration, surgical intervention, and catheter use showed no statistically significant differences between the two groups (Table 2).

Table 2. Clinical characteristics of patients

Variables	COVID-19 pandemic		p
	Restriction period (group 1) n=64	Relaxed period (group 2) n=38	
COVID-19 infection, n (%)	39 (60.9)	14 (36.8)	0.024*
Sleep deprivation, n (%)	56 (87.5)	26 (68.4)	0.037*
Hypoxemia, n (%)	34 (53.1)	27 (71.1)	0.096
Organ failure, n (%)	2 (3.1)	3 (7.9)	0.358
Bladder catheter, n (%)	9 (14.1)	9 (23.7)	0.284
Central venous catheter, n (%)	4 (6.3)	2 (5.3)	0.136
Anemia	34 (53.1)	26 (68.4)	0.149
Hyperglycemia, n (%)	38 (59.4)	21 (55.3)	0.836
Body temperature, n (%)			
Normal	41 (64.1)	25 (65.8)	0.763
Hypothermia	2 (3.1)	2 (5.3)	
Hyperthermia	21 (32.8)	11 (28.9)	
Renal failure, n (%)	12 (18.8)	8 (21.1)	0.801
Dehydration, n (%)	6 (9.4)	4 (10.5)	0.999
Surgical intervention, n (%)	14 (21.9)	7 (18.4)	0.802
Delirium duration, days	3 (2-4)	2 (1-3)	0.045*
Hospital stay, days	9 (6-12)	6 (4-10)	<0.001*
Mortality, n (%)	12 (18.8)	4 (10.5)	0.400

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). * p<0.05 shows statistical significance

DISCUSSION

To the best of our knowledge, this is the first study to examine the factors predisposing to delirium during the COVID-19 restriction and relaxation periods. Despite similar demographic characteristics, the study found notable differences in several clinical and physiological parameters between the groups during the restriction period and the relaxed period of the COVID-19 pandemic. Patients hospitalized during the strict COVID-19 restrictions had a significantly higher rates of COVID-19 infection, more frequent sleep deprivation, and a longer delirium episodes compared to those admitted during the relaxed period.

Studies carried out before the COVID-19 pandemic recognized delirium as a well-established complication in hospitalized older adults, associated with long-term cognitive and functional decline.[18-20] Previous studies have emphasized various factors that predispose older adults to delirium, such as advanced age, preexisting cognitive or functional impairments, sensory deficits (vision or hearing), and multiple chronic conditions.[21-23] In our study, these predisposing factors were present in the majority of cases, consistent with previous studies. However, we found no significant difference in the distribution of these predisposing factors between the restriction and relaxed periods of the COVID-19 pandemic.

Delirium has been identified as a serious complication of COVID-19, associated with poorer outcomes such as higher in-hospital mortality, increased ICU admissions, longer hospital stays, and more in-hospital complications.[24-26] During the COVID-19 pandemic, the recognition and treatment of delirium were further complicated by staff shortages, the use of personal protective equipment, strict isolation measures with limited visitation, and the heightened use of sedative medications.[27] COVID-19 quarantine measures have been associated with adverse psychological effects in the general population.[28] Sun and colleagues conducted a qualitative study on the psychological experiences of COVID-19 patients during hospitalization, finding that in the early stages of the disease, emotions such as anger, anxiety, and worry were prevalent, while psychological states such as loneliness, anxiety, helplessness, and depression emerged during the quarantine period.[29] In Japan, a study examined the incidence of delirium in emergency department patients during the COVID-19 pandemic, comparing the periods before and after visitor restrictions were enforced. The study reported a 3.79-fold increase in delirium incidence after the restrictions.[30] In the present study, during the restriction period of the COVID-19 pandemic, the frequency of delirium cases, as well as the occurrence of COVID-19 infection in these cases, was higher. The combination of social isolation and quarantine, particularly in the absence of family members, is thought to increase the risk of delirium.[25] As normal visitation policies resume compared to the early pandemic, involving family members in delirium prevention strategies, such as the Family-Augmented-HELP program, may improve the effectiveness of delirium prevention in hospitals.[31] These may explain the higher frequency of delirium during the restriction period. Additionally, as restrictions were anticipated during the peak periods of COVID-19 infection, a higher rate of COVID-19 infection may have been observed in delirium cases during these times. Conversely, during the relaxation period, patients may have acquired community immunity through vaccination programs. However, this study lacked information on the vaccination status of the patients.

Another factor connected to delirium is the presence of sleep disorders.[32] The mechanism of delirium remains incompletely understood, but a leading hypothesis involves neurotransmitter imbalance, particularly in the regulation of dopamine, acetylcholine, and tryptophan.[33,34] This same imbalance is also commonly observed in cases of sleep deprivation, further linking disrupted sleep patterns to the development of delirium.[35] Moreover, disturbances in these neurotransmitter systems, particularly within the serotonergic system, are thought to influence both immune function and inflammatory responses, which may increase susceptibility to severe cases of COVID-19.[36] In fact, it has been reported that 85.4% of patients hospitalized with COVID-19 who developed delirium experienced alterations in their sleep-wake cycle, highlighting the close relationship between sleep disruption and cognitive decline.[37] In the present study, during the restriction period of the pandemic, we found a significantly higher frequency of sleep deprivation compared to the relaxed period, which likely contributed to the prolonged delirium episodes observed in our patient population. These findings are consistent with prior research indicating a rise in sleep problems during the pandemic period, compared to pre-pandemic period, in both the general population and hospitalized individuals.[38-41] A study of 1,062 participants in Italy found that sleep disturbances, depression, and anxiety worsened during the COVID-19 quarantine periods, but two years later, subjective sleep quality improved, and

both sleep disturbances and sleep onset latency decreased. It was also noted that the improvement in sleep disorders was accompanied by a decline in depressive and anxiety symptoms.[42] This findings underscores the importance of addressing sleep disturbances in delirium management, particularly during periods of heightened stress, such as the COVID-19 pandemic.

Another important finding of this study was that both delirium duration and hospital stay were significantly longer during the restriction period compared to the relaxed period. The extended hospital stay could be attributed to the higher rates of COVID-19 infection and sleep deprivation during the restriction period, potentially contributing to more prolonged and severe delirium episodes. Prolonged hospital stays are associated to worse patient outcomes, including a higher risk of developing complications such as delirium.[43] Additionally, while the mortality rate during the restriction period was higher, this difference did not reach statistical significance. This non-significant trend suggests that, even in non-ICU settings, factors such as prolonged delirium episodes and complications associated with COVID-19 could have contributed to the higher mortality rate.

Limitations

This study has several limitations that should be taken into account. First, the single-center, retrospective design limits the generalizability of our findings. Since the study was conducted at one hospital, the results may not reflect the experiences of different healthcare settings, patient populations, or regions that experienced different degrees of COVID-19 impact and restrictions. Additionally, the lack of consistent data on the use of standardized tools for delirium diagnosis, such as the Confusion Assessment Method (CAM), is a limitation. Second, patients in the ICU were excluded from the study. ICU patients tend to experience more severe forms of delirium due to factors such as mechanical ventilation, sedation, and organ dysfunction. Including ICU patients might have revealed different patterns and more severe risk factors for delirium, providing a broader perspective on the impact of COVID-19 and associated restrictions on patients with critical illness. Third, the lack of data regarding vaccination status may have influenced the differences in COVID-19 infection rates between the restriction and relaxed periods. Additionally, we did not collect detailed data on the medications used by the patients. Certain medications, such as sedatives or antipsychotics, may affect the development of delirium.[44-46] Finally, more systematic evaluation of psychosocial factors, such as through psychological surveys or assessments, could have provided a clearer understanding of how social isolation influenced delirium development. Future studies incorporating multicenter data, ICU populations, vaccination status, and more comprehensive assessments of psychosocial factors could offer more detailed insights into the wide range of delirium risk factors during pandemic periods. This, in turn, may contribute to the development of more effective prevention strategies.

CONCLUSION

During the restriction period of the COVID-19 pandemic, patients with delirium exhibited higher rates of COVID-19 infection, increased sleep deprivation, and longer delirium episodes compared to those during the relaxed period. Although other predisposing factors such as age and comorbidities were similar between the two periods, the prolonged delirium duration and extended hospital stays observed in the restriction period suggest that environmental and psychosocial factors may have contributed to more severe outcomes. This indicates that stressors like social isolation and the absence of family support during strict pandemic restrictions could have exacerbated the severity of delirium.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the İstanbul Atlas University Medicine Hospital Clinical Researches Ethics Committee (Date: 18.12.2023, Decision No: 10/31).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author declare they have no conflicts of interest.

Financial Disclosure

The author declared that this study has received no financial support.

Author Contributions

The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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